



ITW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Group Art Unit: 1632

MAURICE ARTHUR TREWHELLA et al

Authorized Officer:

Serial No.: 10/814,891

Filed: March 31, 2004

For: **NEW CONDITIONS FOR REACTIONS
MEDIATED BY YEAST**

Attorney Docket No.: GRH0105PUSA

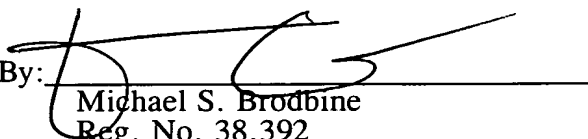
TRANSMITTAL LETTER

Commissioner for Patents
U.S. Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

With regard to the above-identified U.S. National application, enclosed is the priority document for Australian Application No. 2003905675 filed October 16, 2003.

Respectfully submitted,
MAURICE ARTHUR TREWHELLA et al

By: 
Michael S. Brodbine
Reg. No. 38,392
Attorney/Agent for Applicant

Date: August 2, 2004
BROOKS KUSHMAN P.C.
1000 Town Center, 22nd Floor
Southfield, MI 48075
Phone: 248-358-4400
Fax: 248-358-3351

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this paper, including all enclosures referred to herein, is being deposited with the United States Postal Service as first-class mail, postage pre-paid, in an envelope addressed to: Commissioner for Patents, U.S. Patent & Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 on:

August 2, 2004
Date of Deposit

Maria Katirtzidakis
Name of Person Signing


Signature



Patent Office
Canberra

I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003905675 for a patent by VICTORIA UNIVERSITY OF TECHNOLOGY and POLYCHIP PHARMACEUTICALS PTY LTD as filed on 16 October 2003.

WITNESS my hand this
Twenty-fifth day of March 2004

JULIE BILLINGSLEY
TEAM LEADER EXAMINATION
SUPPORT AND SALES



AUSTRALIA
Patents Act 1990

PROVISIONAL SPECIFICATION

Applicant(s):

VICTORIA UNIVERSITY OF TECHNOLOGY

POLYCHIP PHARMACEUTICALS PTY LTD
A.C.N. 006 455 456

Invention Title:

NEW CONDITIONS FOR REACTIONS MEDIATED BY YEAST

The invention is described in the following statement:

NEW CONDITIONS FOR REACTIONS MEDIATED BY YEAST

The present invention relates to new environments in which to conduct certain classes of chemical reactions.

5 The present invention particularly relates to new methods and environments for the synthesis of useful pharmaceutical compounds such as aryloxy phenyl propylamines (eg. Prozac; Trade Mark of Eli Lilly, Inc.), 2-aryl ethylamines (eg ephedrine) and propionic acid

10 derivatives (eg. ibuprofen), especially in an enantiomerically-pure form.

BACKGROUND TO THE INVENTION

15 Due to the complex molecular structure of many organic compounds which have pharmacological activity, it is common for pharmaceutically-useful agents to include one or more chiral centres. The complex structure of such compounds means that their synthesis involves many steps,

20 and consequently where chiral centres are present, the compounds are usually prepared in the form of racemic mixtures.

The pharmacological activity of the compound is

25 often mediated by the binding of the pharmacological agent to a target site. The more accurate the 3-dimensional fit between the pharmacological agent and the target site, the more potent the pharmacological activity, and the lower the likelihood of unwanted side-effects.

30 As a consequence of this, it is not unexpected that individual enantiomeric forms of a chiral compound show different pharmacological activity, differences in metabolic behaviour and different spectra of undesirable

35 side-effects.

It is therefore highly desirable to ensure as far

as possible that the end-products of synthesis of pharmaceutical compounds are enantiomerically pure.

Physicochemical methods for production of
5 enantiomerically pure compounds usually involve multi-step
synthesis incorporating one or more steps which are
asymmetric, and laborious purification procedures. Such
methods are not only tedious, but frequently provide
relatively poor yields. Alternatively enantiomerically-
10 pure starting materials can be used, together with
enantioselective reaction steps; however, such pure
starting materials are available only for a very limited
number of desired compounds.

15 In recent years, intense efforts have been
directed towards development of methods which are highly
selective, provide a good rate of transformation, and
enable easy, non-chromatographic separation and
purification of the product. It has also been considered
20 particularly desirable for the reactions to be carried out
in non-aqueous solvents, since these are particularly
convenient for large scale reactions and purifications.

Some principle candidate classes of
25 pharmaceutical compounds containing chiral centres which
may be advantageously stereospecifically synthesised
include aryl ethylamines such as ephedrine and the other
sympathomimetic amines, aryl propylamines such as
fluoxetine (Prozac) and the other serotonin selective
30 uptake inhibitors, and propionic acid derivatives such as
ibuprofen, naproxen and fenoprofen.

Ephedrine (α -[1-(methylamino)ethyl]benzene-
methanol), originally isolated from plants of the genus
35 *Ephedra*, occurs as the naturally-occurring isomers
l-ephedrine and d-pseudoephedrine, and other
pharmacologically active isomers include d-ephedrine and

l-pseudoephedrine. These compounds are adrenergic sympathomimetic agents and have antihistamine activity; *l*-ephedrine is widely used as a bronchodilator, while *d*-pseudoephedrine is widely used as a decongestant.

- 5 Compounds of these groups are present in a very wide range of prescription and over-the-counter pharmaceutical formulations.

10 The production of *l*-phenylacetylcarbinol (PAC), a precursor of *l*-ephedrine, by catalysis using whole baker's yeast cells in aqueous medium was one of the first microbial biotransformation processes to be used commercially. This reaction included the yeast-mediated reduction of a ketone intermediate to produce the chiral
15 phenylacetylcarbinol, although today the more common synthetic route involves yeast-mediated condensation between benzaldehyde and pyruvate to form PAC.

The yeast-catalysed systems have utilised aqueous
20 solvent systems, which have been found to be inconvenient for large-scale extraction and purification. Additional problems associated with the aqueous solvent systems are the low yields and low purity. Whilst the reaction has been improved by utilising immobilised cells, or cells
25 which have been selected or genetically modified, this adds significantly to the cost of the process. The use of purified enzymes is normally prohibitively expensive, and again without the use of immobilised enzymes the yields tend to be low and purification difficult. In view of the
30 difficulty of large-scale extraction and purification with the aqueous solvent systems, organic systems, supercritical fluid systems and liquefied gas systems have been investigated.

35 In our earlier International Application PCT/AU00/01543, we showed that yeast-mediated acyloin condensation of benzaldehyde can be achieved in

supercritical or liquefied carbon dioxide or in liquefied petroleum gas. The use of supercritical fluids as the reaction medium in large scale reactions is advantageous as compared with conventional organic solvents since the purification and processing of the products is simpler. However, the use of such reagents requires specialised equipment design and control which can be quite complex and expensive.

There is accordingly still room for the current systems for synthesising pharmaceutical compounds (stereoselectively) to be improved upon.

It has now been surprisingly found by the present applicant that yeast mediated reduction reactions of organic compounds can be conducted in the absence of a solvent. The present applicant has established that a broad range of important pharmaceutical compounds containing chiral centres can be stereoselectively synthesised using a synthetic route in which a starting compound is subjected to a yeast-mediated reduction reaction to provide an enantiomerically pure precursor, which can then be converted into one isomer of the target pharmaceutical compound.

SUMMARY OF THE INVENTION

According to one aspect of the present invention there is provided a method of reducing an organic compound, comprising subjecting the organic compound to a yeast mediated reduction wherein the reduction is conducted in the absence of a solvent.

It will be understood to a person skilled in the art that the yeast mediated reaction requires some water for the reaction to take place. Sufficient water is required for enzymes to be hydrated and take the

appropriate configuration. A "monolayer" of water around the enzymes is required. For many compounds, the presence of larger volumes of water (ie sufficient water to provide a separate water layer) prevents or substantially prevents the yeast-mediated reduction of that compound from taking place. This is particularly the case for water-insoluble organic compounds. In contrast, the applicant has surprisingly found that these water-insoluble compounds react rapidly and with high yield when simply mixed with near-dry or damp yeast (ie yeast with insufficient water to provide a visible separate water layer). This level of water corresponds to a water-to-yeast ratio of up to 1.5 ml/g (approximately 60% w/w). The minimum amount of water required is approximately 0.2 ml/g of yeast (approximately 10% w/w). Dry yeast contains at most 1-3% w/w water, and therefore must be wetted to be activated for use according to the present invention. Preferably, the water to yeast ratio is 0.8 to 1.2 ml/g of yeast (approximately 44 to 55% w/w).

20

Whilst water is sometimes used as a solvent in organic reactions (particularly for reactions involving water-soluble organic reagents), according to the present invention water is not used in a high enough volume to function as a solvent. Accordingly, it is to be understood that the water is not a solvent in the context of the present application.

Any yeast capable of effecting the reduction reaction may be used. It is economically advantageous to use the cheapest yeast available, and ordinary baker's yeast, *Saccharomyces cerevisiae*, is preferred. Strains of yeast adapted to other purposes, including brewing yeast and wine or sherry yeasts could also be employed. For maximum efficiency of reaction, it is advisable to present the maximum surface area of yeast for contact with the reactants. This can be effected by using "active" dried

35

yeast, which is readily commercially available as "instant dry yeast", and may be stored at room temperature. Alternatively, well-pulverised dry baker's yeast may be used. Typically "dry yeasts" have 1-3% w/w water. Other
5 yeasts, such as those described in United States Patent No. 4,734,367, or fungi such as those disclosed in Chênevert et al (1992) (Chênevert, R. Fortier, G. and Rhlid, R.B., Tetrahedron, 1992 48 6769-6776) may also be used. The person skilled in the art will readily be able
10 to test whether any specific organism will function for the purposes of the invention, using the methods described herein.

The yeast mediated reduction reaction is
15 significantly faster than prior art methods and also provides an improved result. The applicant has achieved greater than 80% isolated yield as a result of complete reduction of the organic compound. Little or no side products are produced. No side products have been
20 detected in the products of the reaction by the present applicant.

The proportion of yeast to organic compound may be anything from 0.1 gram of yeast per mmol of organic
25 compound, up to 50 grams of yeast per mmol of organic compound. However, the preferred range is 1 to 20 g/mmol. While it is possible to speed up the reaction by the use of extra yeast, this is usually unnecessary.

30 The reaction is carried out in non-fermenting conditions at temperatures between 0 to 50°C. For optimum results, the reaction is carried out at room temperature. Usually the reaction is conducted at atmospheric pressure, although it is noted that the reaction is not affected by
35 changes in pressure.

Preferably, the method of the invention involves

contacting the organic compound with the yeast and water to form a mixture, leaving the mixture for sufficient time for the reaction to take place, adding an organic solvent to the mixture to dissolve the product of the reaction
5 into the organic solvent, and conducting a solid/liquid separation to separate the product of the reaction from the yeast. Preferably the solvent is evaporated to yield the product of the reaction.

10 The water that is present in the mixture is present in such a small amount that it "sticks" to the yeast, and does not interfere with the removal of the product of the reaction (an organic compound) into the organic solvent. It is a significant advantage of the
15 method of the invention that a biphasic (aqueous/organic) extraction is avoided. Biphasic extractions are often associated with low isolated yields. It is also an advantage of the invention that no reagents (in this case, the water/yeast) are extracted into the organic solvent,
20 so that no separate purification steps are required.

A broad range of organic compounds can be reduced using the method of the present invention. Specific classes of compounds that may be reduced by the reaction
25 include ketones, alkenes, alkynes, aldehydes, imines (ie compounds containing the group $-C=N-$) and hydroxamines.

The reaction is most effective on conjugated or activated ketones and alkenes.

30

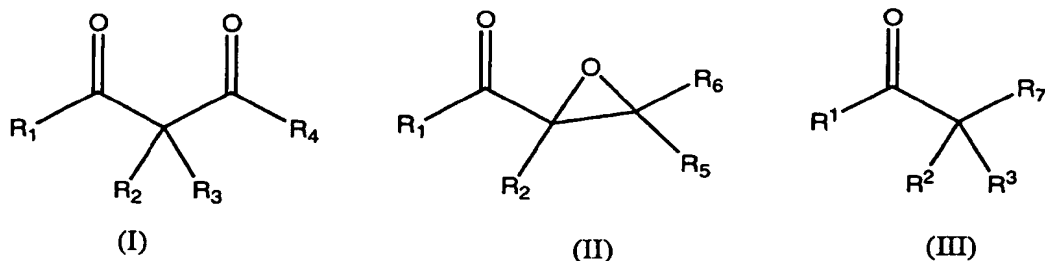
Consequently, particularly suitable classes of organic compounds for subjecting to the method of the present invention are β -keto amides, β -keto esters, enol ethers, activated ketones and conjugated (activated)
35 alkenes (ie alkenes with an atom with an electrophilic character, as may be provided, for example by alkenes substituted with NO_2 , $-CN$, ketone, ester, amide, aldehyde,

thioether, alkene, aromatic groups, halogens, etc).

Amongst these organic compounds, some classes are industrially very useful precursors in the stereoselective synthesis of known pharmaceutical agents. Particularly
5 suitable classes of organic compounds which may be reacted according to the method of the invention to form useful precursor compounds include the following:

Activated ketones (I), (II), and (III):

10



in which:

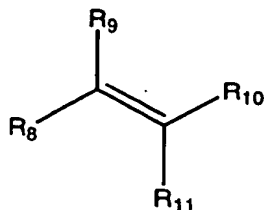
R_1 is an optionally substituted aryl group;

15 R_2 , R_3 , R_5 and R_6 are H or optionally substituted $C_1 - C_6$ alkyl;

R_4 is an optionally substituted $C_1 - C_6$ alkoxy, aryloxy, amino, optionally substituted di- $(C_1-C_6$ alkyl)amino, optionally substituted alkaryl amino optionally substituted
20 $C_1 - C_6$ alkyl amino, optionally substituted cyclic amino, such as pyrrolidino, piperidino, imidazolidinyl, piperazinyl, morpholinyl, C_{1-6} alkylpyrrolidino or C_{1-6} alkylpiperidino; and

R_7 is cyano; nitro; halo; OH; NH_2 ; C_{1-6} alkyl substituted by
25 OH, halo, amine, or C_{1-6} alkyl amino;

Conjugated alkenes:



(IV)

wherein:

- 5 R₈ is an optionally substituted aromatic group;
R₉, R₁₀ and R₁₁ are each independently selected from H,
hydroxy, C₁₋₆alkoxy, mercapto, C₁₋₆ alkylthio, amino, C₁₋₆
alkylamino, di(C₁₋₆alkyl)amino, carboxy, C₁₋₆alkoxycarbonyl,
C₁₋₆aryloxycarbonyl, carbamoyl, C₁₋₆alkylcarbamoyl, di-C₁₋₆
10 alkylcarbamoyl, C₁₋₆cycloalkylcarbamoyl, C₁₋₆alkylsulphonyl,
arylsulphonyl, C₁₋₆alkylaminosulphonyl, di(C₁₋₆
alkyl)aminosulphonyl, nitro, cyano, cyano-C₁₋₆alkyl,
hydroxyC₁₋₆alkyl, amino-C₁₋₆alkyl, C₁₋₆alkanoylamino, C₁₋₆
alkoxycarbonylamino, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, C₁₋₆
15 alkyl, halo, haloC₁₋₆alkyl, or haloC₁₋₆alkoxy, alkoximino,
hydroximino, and alkylimino.

To generate a new chiral centre, one of R₉, R₁₀
and R₁₁ must not be H. Accordingly, preferably at least
20 one of R₉, R₁₀ and R₁₁ is not H.

For the compounds of formulae (I), (II) and
(III), R₁ is preferably substituted or unsubstituted phenyl
or 2-thienyl. The phenyl group may contain one or more
25 substituents, preferably selected from hydroxy, methyl,
methoxy, hydroxymethyl and trifluoromethyl.

For the compounds of formulae (I), (II) and
(III), R₂ is preferably H, and R₃ is preferably either H,
30 methyl or ethyl. Most preferably R₃ is also H.

R₄ in the compound of formula (I) is preferably methoxy, ethoxy, C₁₋₆ alkylamino, NH₂, or di(C₁₋₆alkyl)amino. More preferably R₄ is NH₂ or C₁₋₆ alkylamino.

R₅ and R₆ in the compound of formula (II) are preferably each H.

Preferably R₇ is cyano, alkylhalo or C₁₋₆ alkylamino.

These compounds of Formula (I), (II) and (III) may be subjected to the method of the present invention to form precursors for the synthesis of serotonin selective uptake inhibitors and related compounds such as fluoxetine (Prozac), tomoxetine, duloxetine, nisoxetine, and each of the compounds defined in US 4,314,081, as well as epinephrine, norepinephrine, ethylnorepinephrine, isoproterenol, isoetharine, metaproterenol, terbutaline, metaproterenol, phenylephrine, ritodrine, prenalterol, methoxamine, albuterol and derivatives with N-substitution such as salmeterol, ephedrine, phenylpropanolamine. The routes to the synthesis of these compounds from the compounds of formulae (I), (II) and (III) are described in further detail below.

The compound of Formula (IV) may be used as the starting compound for the synthesis of the pharmaceuticals listed above, together with amphetamine and its derivatives such as hydroxyamphetamine, methamphetamine, benzphetamine, fenfluramine, propylhexedrine, and propionic acid derivatives, such as ibuprofen, naproxen, alminoprofen, fenoprofen, flurbiprofen, indoprofen, ketoprofen and suprofen.

For the compounds of formula (IV), the aromatic

group R₈ may be substituted or unsubstituted phenyl when the compound is to be used for the synthesis of the sympathomimetic amines and phenylpropylamines such as Prozac. The preferred substituents on the phenyl group
5 are hydroxy, methyl, methoxy, hydroxymethyl and trifluoromethyl. For the synthesis of the propionic acid derivatives referred to above from the compound of formula (IV), the aryl group may be substituted phenyl (such as *p*-isobutyl for ibuprofen, 3-phenoxyphenyl for fenoprofen, 2-
10 fluoro-4-biphenyl for flurbiprofen, 4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)phenyl, 3-benzoylphenyl for ketoprofen, *p*-(2-thenoyl)phenyl for suprofen or *p*-methylallylaminophenyl for alminoprofen) or a substituted naphthyl (such as 6-methoxy-2-naphthyl- for naproxen).
15 Consequently, the substituents on the phenyl and naphthyl groups may be selected from a wide variety of substituents.

For the preparation of propionic acid
20 derivatives, R₁₀ and R₁₁ are preferably each H, and R₉ is carboxy or C₁₋₆alkoxycarbonyl.

For the preparation of one of the more commonly used ethylamines containing a substituent on the α -carbon atom (such as amphetamine) from compound (IV), preferably
25 R₉ is H or hydroxy. Preferably, one of R₁₀ and R₁₁ is selected from C₁₋₆alkyl, and more preferably methyl or ethyl. Preferably the other of R₁₀ and R₁₁ is selected from C₁₋₆alkoxycarbonyl, C₁₋₆aryloxycarbonyl, carbamoyl, C₁₋₆alkylcarbamoyl, di-C₁₋₆alkylcarbamoyl, C₁₋₆cycloalkylcarbamoyl or nitro.
30

For the preparation of one of the more commonly used propylamines containing a substituent on the β -carbon atom (such as fluoxetine) from compound (IV), preferably R₉ is hydroxy. More preferably, one of R₁₀ and R₁₁ is selected
35 from H and C₁₋₆alkyl, and more preferably it is H. Preferably the other of R₁₀ and R₁₁ is selected from cyano, C₁₋₆alkoxycarbonyl, C₁₋₆aryloxycarbonyl, carbamoyl, C₁₋

alkylcarbamoyl, di-C₁₋₆alkylcarbamoyl and C₁₋₆cycloalkylcarbamoyl.

According to the present invention, there is also
5 provided a method of synthesising a pharmaceutical
compound comprising the step of subjecting a precursor to
a yeast mediated reduction wherein the reduction is
conducted in the absence of a solvent; and converting the
product of the reduction reaction into the pharmaceutical
10 compound.

Preferably, the pharmaceutical compound is a
sympathomimetic amine, an ethyl amine, a propylamine or a
propionic acid. More preferably, the pharmaceutical
15 compound is an arylethylamine, an arylpropylamine, or a
propionic acid with a 2-aryl substitution.

Particular pharmaceutical compounds that can be
synthesised via the solvent-free yeast mediated reduction
20 step of the present invention are fluoxetine (Prozac),
tomoxetine, duloxetine, nisoxetine, epinephrine,
norepinephrine, ethylnorepinephrine, isoproterenol,
isoetharine, metaproterenol, terbutaline, metaproterenol,
phenylephrine, ritodrine, prenalterol, methoxamine,
25 albuterol and derivatives with N-substitution such as
salmeterol, derivatives of amphetamine, ephedrine,
phenylpropanolamine, amphetamine and its derivatives such
as hydroxyamphetamine, methamphetamine, benzphetamine,
fenfluramine and propylhexedrine, ibuprofen, naproxen,
30 alminoprofen, fenoprofen, flurbiprofen, indoprofen,
ketoprofen and suprofen.

DETAILED DESCRIPTION OF THE INVENTION:

35 A number of chemical terms used in the above
description of the invention are defined below to avoid
any ambiguity.

The term "alkyl" used either alone or in a compound word such as "optionally substituted alkyl" or "optionally substituted alkylamino" denotes straight
5 chain, branched or mono- or poly- cyclic alkyl, preferably C₁₋₆ alkyl or cycloalkyl. Examples of straight chain and branched C₁₋₆ alkyl include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl,
10 hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl and 1,1,2-trimethylpropyl.

15 The term "aryl" used either alone or in compound words such as "optionally substituted aryl", "optionally substituted aryloxy" or "optionally substituted heteroaryl" denotes single, polynuclear, conjugated and fused residues of aromatic hydrocarbons or aromatic
20 heterocyclic ring systems. Examples of aryl include phenyl, biphenyl, terphenyl, quaterphenyl, phenoxyphenyl, naphthyl, tetrahydronaphthyl, anthracenyl, dihydroanthracenyl, benzanthracenyl, dibenzanthracenyl, phenanthrenyl, fluorenyl, pyrenyl, indenyl, azulenyl,
25 chrysenyl, pyridyl, 4-phenylpyridyl, 3-phenylpyridyl, thienyl, furyl, pyrrolyl, pyrrolyl, furanyl, imadazolyl, pyrrolydiny, pyridinyl, piperidinyl, indolyl, pyridazinyl, pyrazolyl, pyrazinyl, thiazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothienyl,
30 purinyl, quinazolinyl, phenazinyl, acridinyl, benzoxazolyl, benzothiazolyl and the like. Preferably, the aromatic heterocyclic ring system contains 1 to 4 heteratoms independently selected from N, O and S and containing up to 9 carbon atoms in the ring.

35

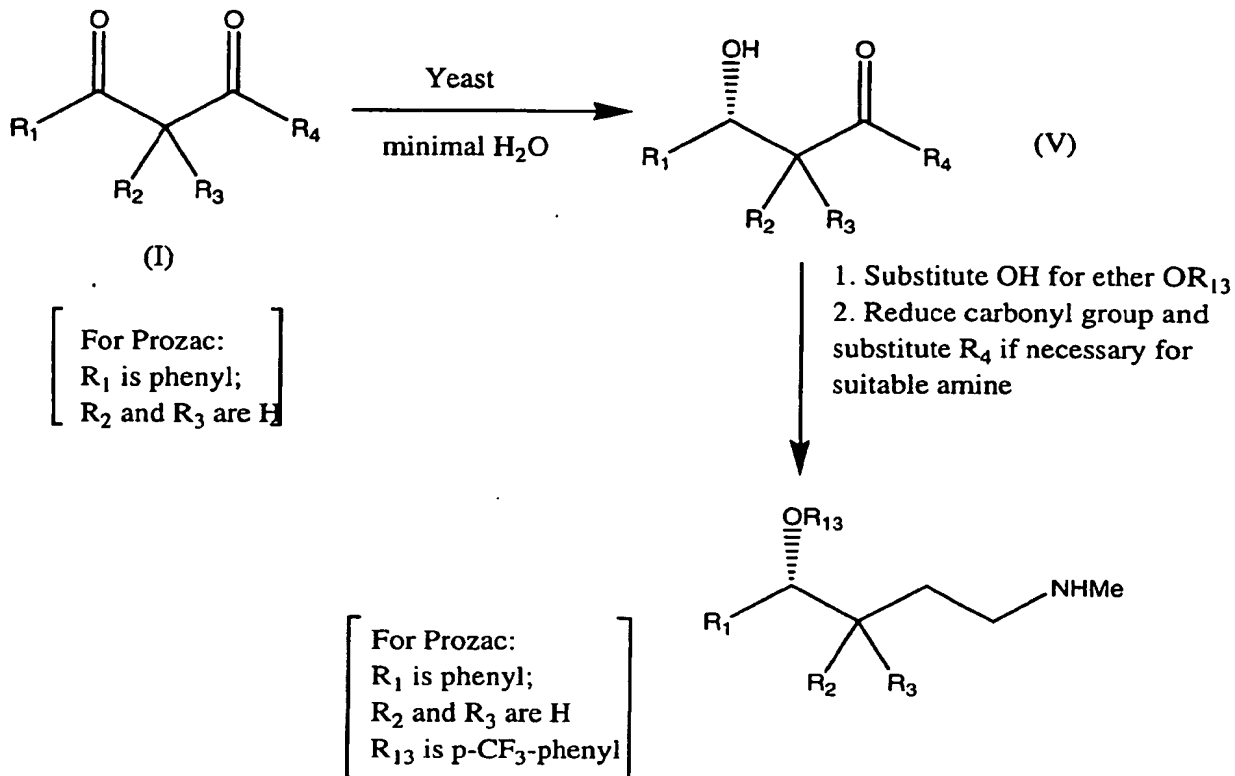
In the description provided above, reference is made to optional substituents. In this specification

"optionally substituted" means that a group may or may not be further substituted with one or more groups selected from alkyl, alkenyl, alkynyl, aryl, halo, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, hydroxy, alkoxy, alkenyloxy, aryloxy, benzyloxy, haloalkoxy, haloalkenyloxy, haloaryloxy, nitro, cyano, nitroalkyl, nitroalkenyl, nitroalkynyl, nitroaryl, nitroheterocyclyl, amino, alkylamino, dialkylamino, alkenylamino, alkynylamino, arylamino, diarylamino, benzylamino, dibenzylamino, acyl, alkenylacyl, alkynylacyl, arylacyl, acylamino, diacylamino, acyloxy, alkylsulphonyloxy, arylsulphenyloxy, heterocyclyl, heterocycloxy, heterocyclamino, haloheterocyclyl, alkylsulphenyl, arylsulphenyl, carboalkoxy, carboaryloxy, mercapto, alkylthio, benzylthio, acylthio, phosphorus-containing groups, azo, imino, nitrile, carboxylate and the like. Preferably the substituents are selected from C₁₋₆ alkyl, halo, trifluoromethyl, hydroxy, and C₁₋₆alkoxy.

20 EXAMPLES

The following reaction schemes are provided to illustrate how the method of the present invention can be incorporated into a reaction scheme for the stereoselective synthesis of a target pharmaceutical compound. The specific compounds referred to above have similar structures with different substituents, and methods for their synthesis are well known. The known synthetic methods can be modified to incorporate the new solvent-free yeast mediated stereoselective reduction step of the present invention in one of the following ways.

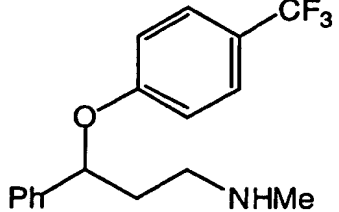
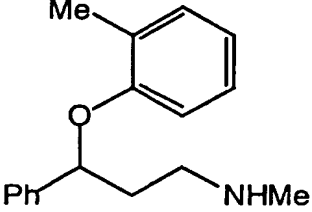
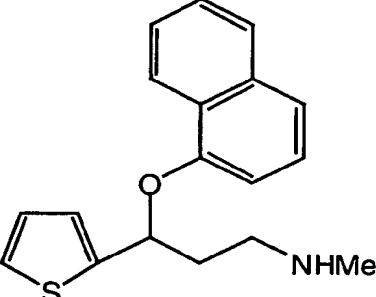
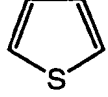
1. Preparation of Prozac (as one example) from β -keto esters or amides.



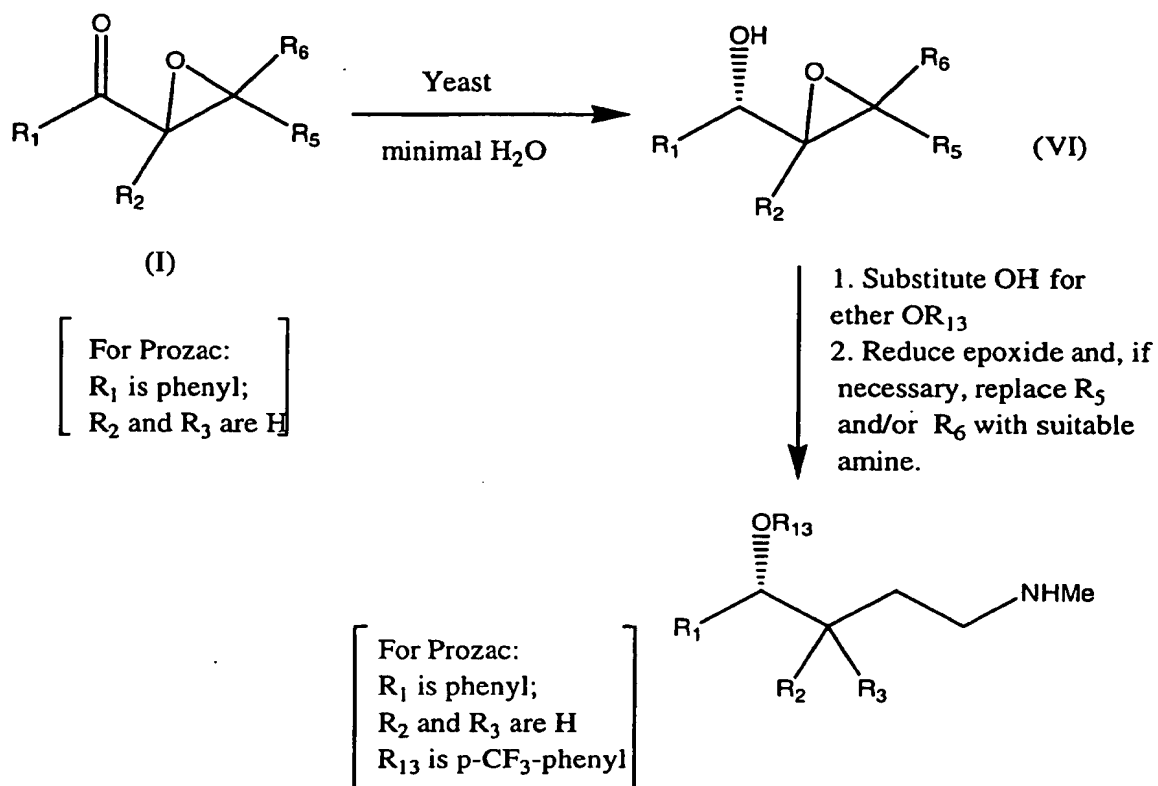
The above reaction scheme illustrates the synthesis of Prozac from a β -keto ester or amide, in accordance with the present invention. Suitable reagents and reaction conditions for conducting the steps following the yeast mediated reduction are outlined in *J. Org. Chem* 53 (17) 4081, particularly for the situation where R_4 is $-\text{CH}_2\text{OH}$.

Other propylamines can be synthesised using this technique by using the appropriate reagents. Table 1 details suitable target propylamines.

Table 1

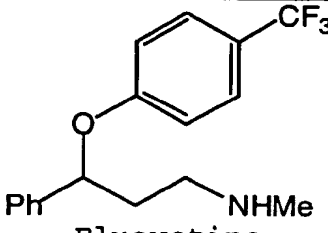
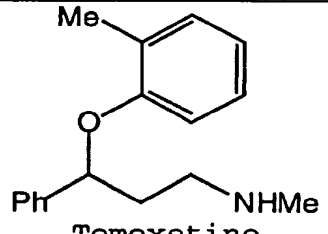
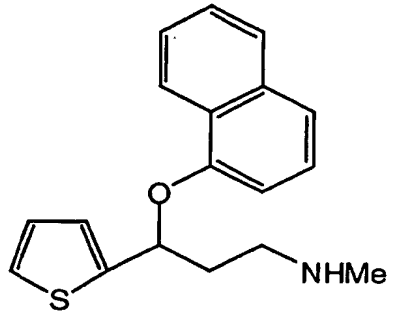
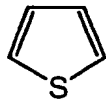
Compound	R ₁	R ₂	R ₃
 Fluoxetine	Ph	H	H
 Tomoxetine	Ph	H	H
 Duloxetine Nisoxetine		H	H
		H	H

2. Preparation of Prozac from β -keto epoxide:

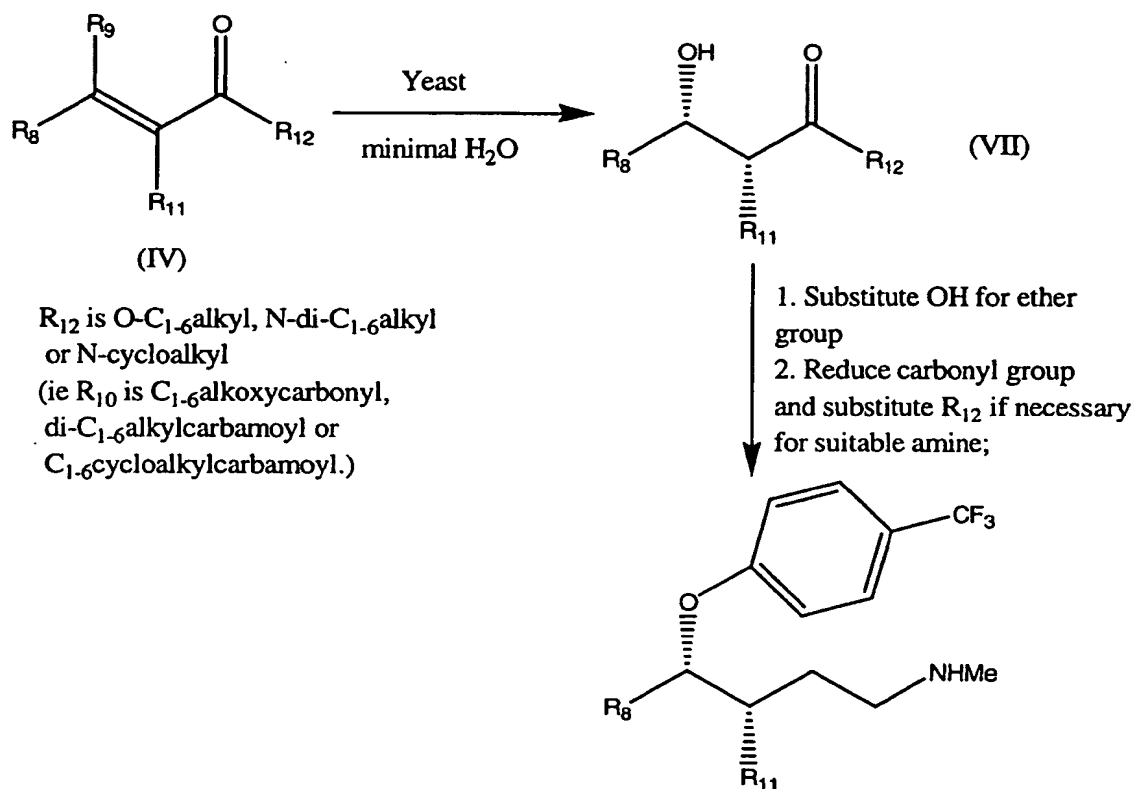


5 Similarly to method 1 outlined above, this method can be applied to the synthesis of the compounds outlined in Table 2. See *J. Org.Chem.* 53(17) 4081.

Table 2

Compound	R ₁	R ₂	R ₅	R ₆
 Fluoxetine	Ph	H	H	H
 Tomoxetine	Ph	H	H	H
 Duloxetine Nisoxetine		H	H	H
		H	H	H

3. Preparation of Prozac from enol ether of β -keto ester



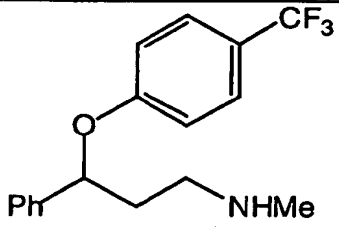
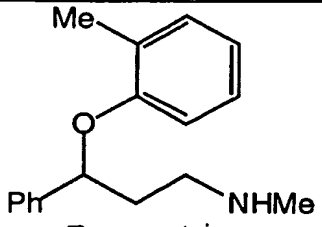
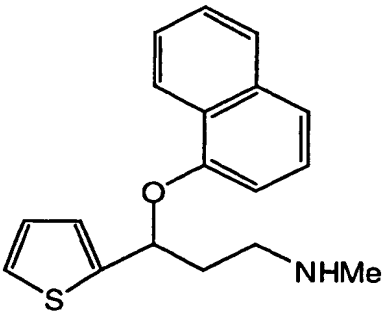
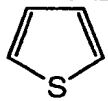
5

Again, aside from the yeast-mediated reduction step, appropriate reaction reagents and conditions are set out in *J. Org. Chem.* 53(17) 4081. The yeast-mediated reduction is conducted in accordance with the procedure outlined in the Experimental section.

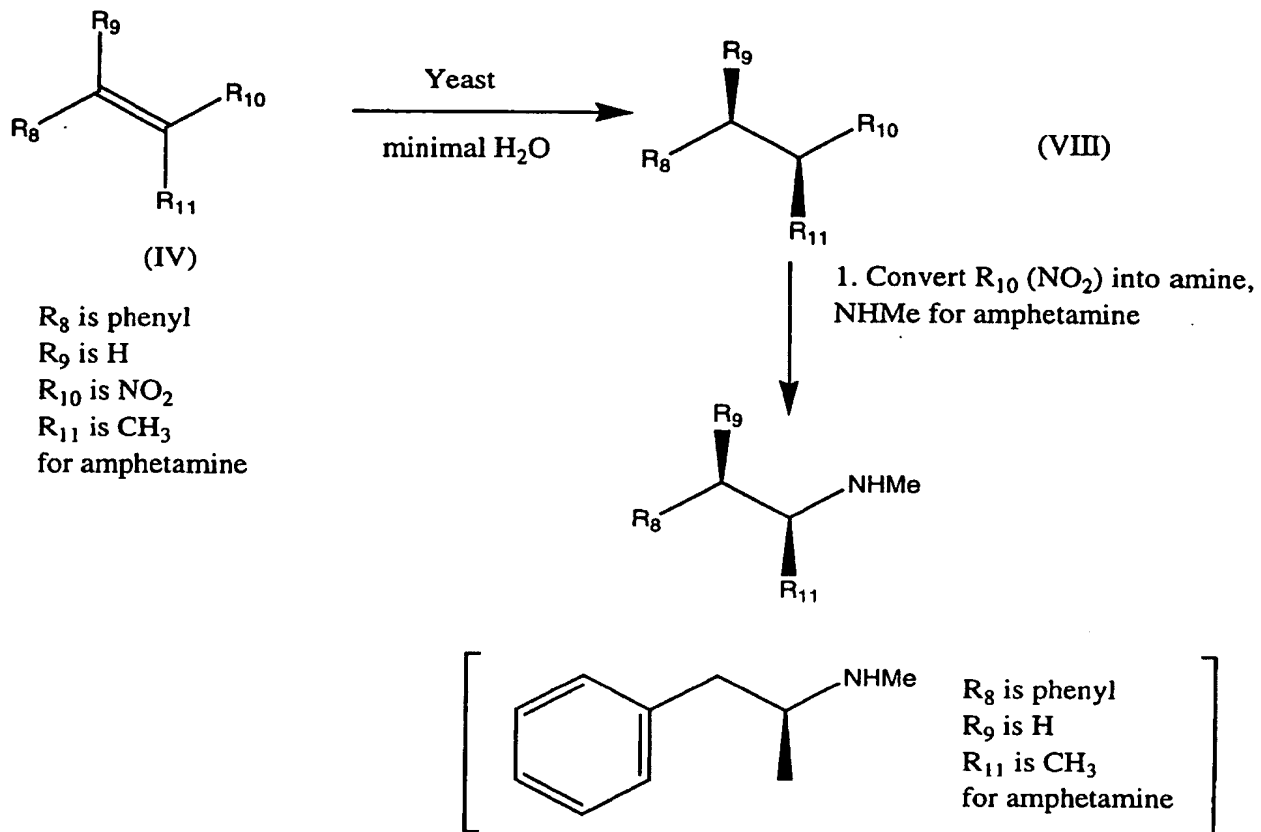
10

This procedure can also be used for the synthesis of the compounds outlined in Table 3.

Table 3

Compound	R ₈	R ₂	R ₁₁
 Fluoxetine	Ph	H	H
 Tomoxetine	Ph	H	H
 Duloxetine Nisoxetine		H	H
		H	H

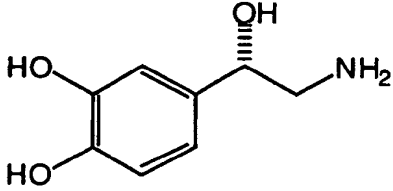
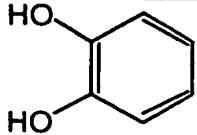
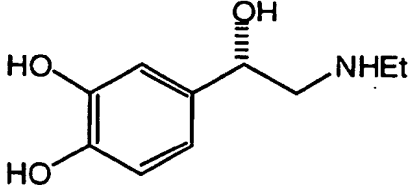
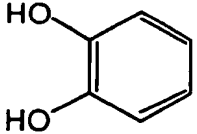
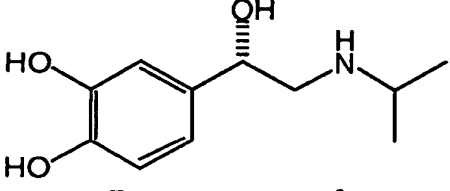
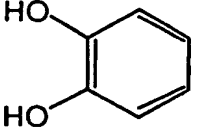
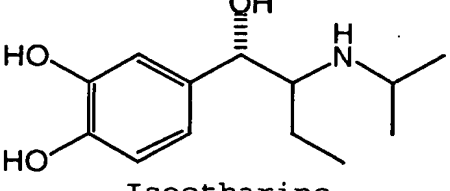
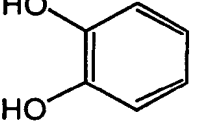
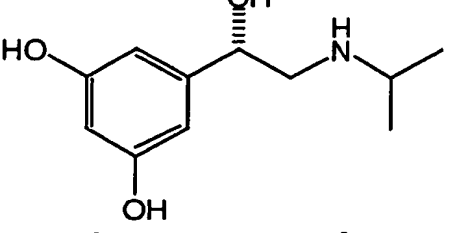
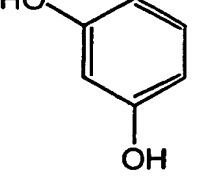
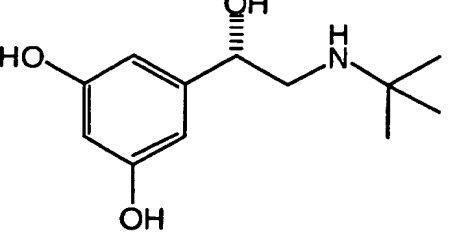
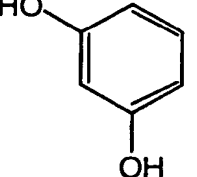
4. Preparation of amphetamine from conjugated alkene:

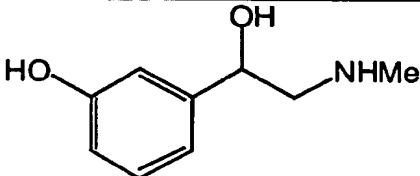
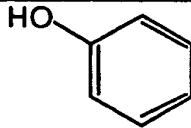
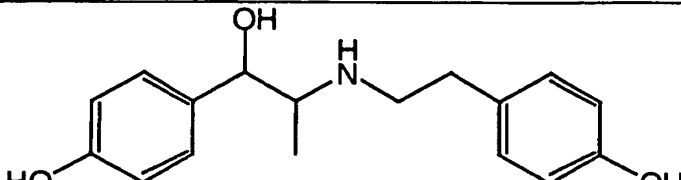
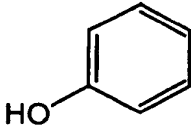
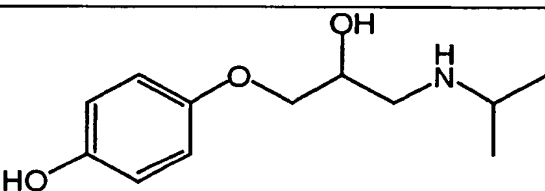
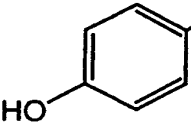
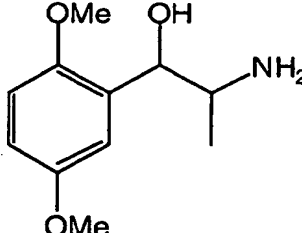
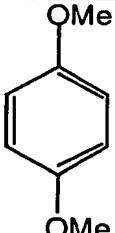
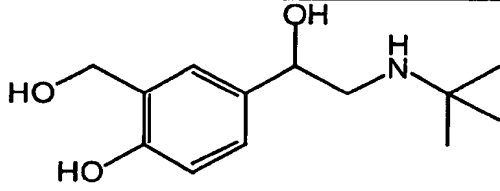
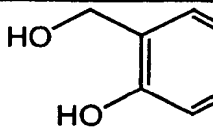
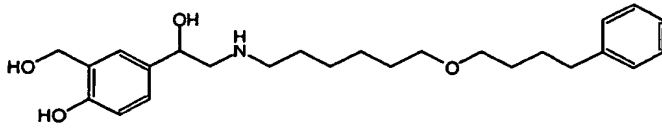
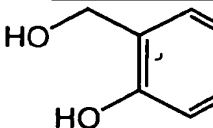
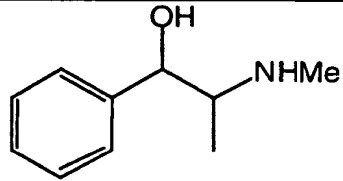


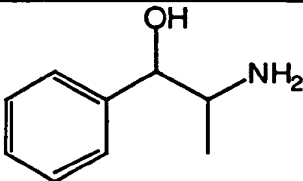
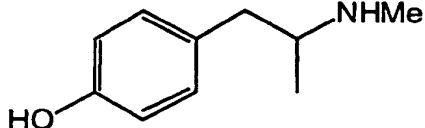
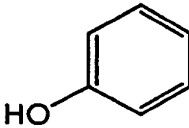
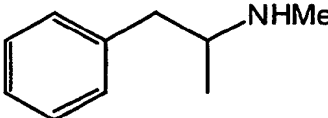
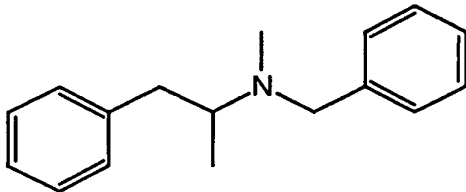
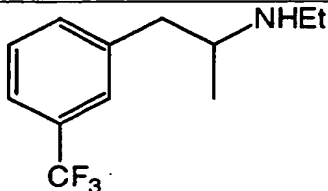
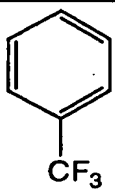
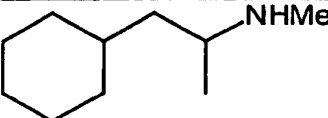
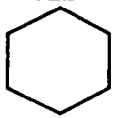
The procedure outlined above can likewise be utilised for the synthesis of the compounds outlined in the Table 4.

Table 4

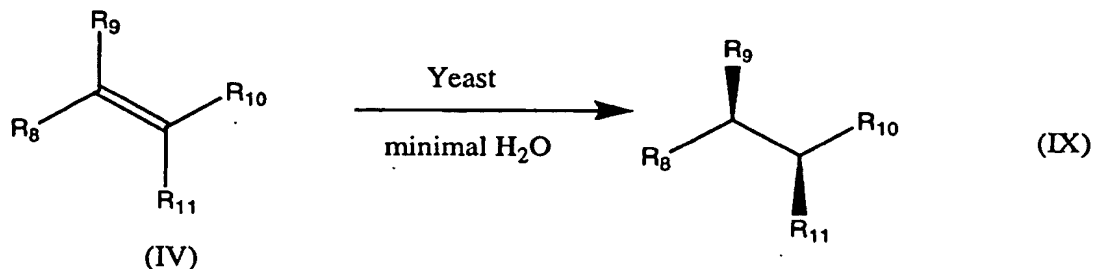
Compound	R ₈	R ₉	R ₁₀	R ₁₁
 Amphetamine	Ph	H	NO ₂	CH ₃
 Epinephrine	HO HO	OR	NO ₂	H

 Nor epinephrine		OR	NO ₂	H
 Ethylnorepinephrine		OR	NO ₂	H
 Isoproterenol		OR	NO ₂	H
 Isoetharine		OR	NO ₂	
 Metaproterenol		OR	NO ₂	H
 Terbutaline		OR	NO ₂	H

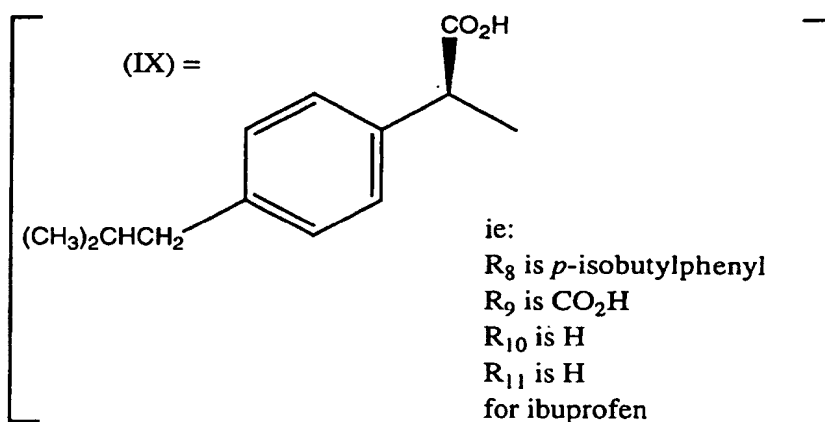
 <p>Phenylephrine</p>		OR	NO ₂	H
 <p>Ritodrine</p>		OR	NO ₂	CH ₃
 <p>Prenalterol</p>		OR	NO ₂	H
 <p>Methoxamine</p>		OR	NO ₂	CH ₃
 <p>Albuterol</p>		OR	NO ₂	H
 <p>Salmeterol</p>		OR	NO ₂	H
 <p>Ephedrine</p>	Ph	OR	NO ₂	CH ₃

 Phenylpropanolamine	Ph	OR	NO ₂	CH ₃
 Hydroxyamphetamine		H	NO ₂	CH ₃
 Methamphetamine	Ph	H	NO ₂	CH ₃
 Benzphetamine	Ph	H	NO ₂	CH ₃
 Fenfluramine		H	NO ₂	CH ₃
 Propylhexedrine		H	NO ₂	CH ₃

5. Preparation of ibuprofen

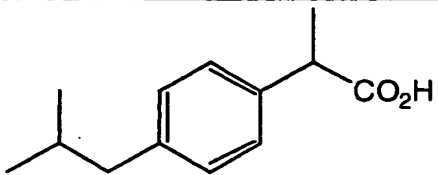
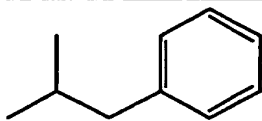
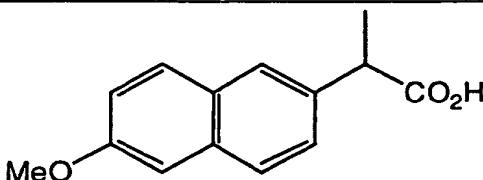
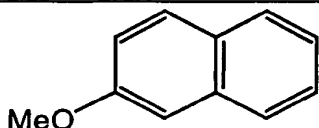
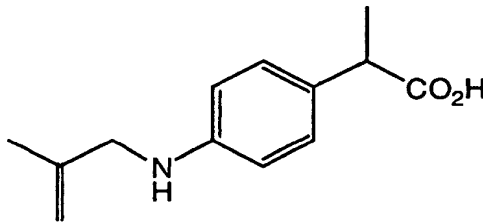
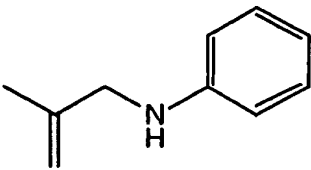
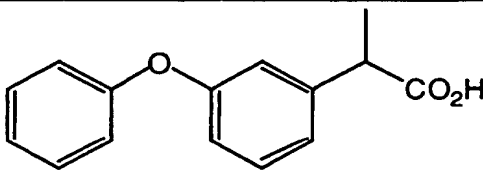
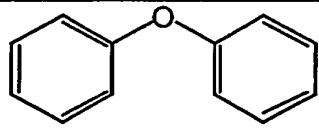
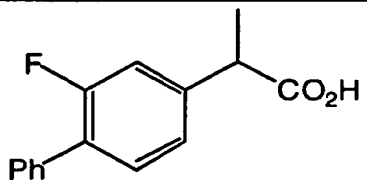
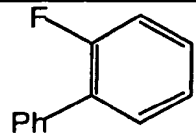
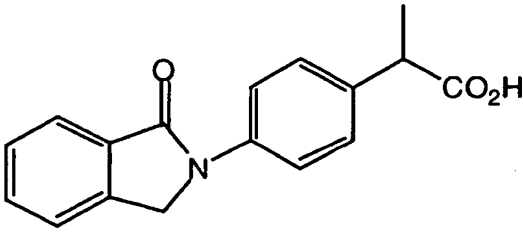
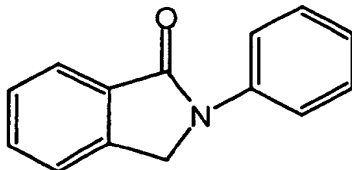


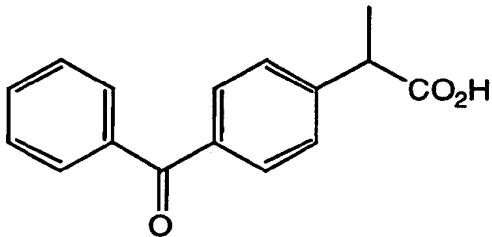
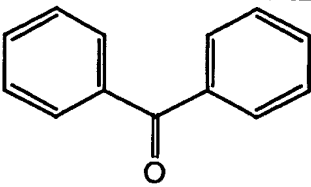
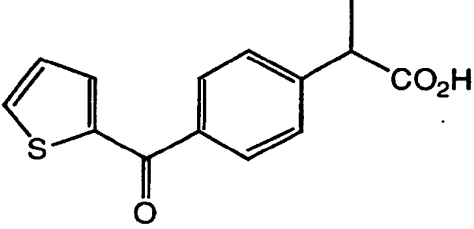
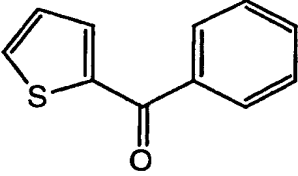
R_8 is *p*-isobutylphenyl
 R_9 is CO_2H
 R_{10} is H
 R_{11} is H
 for ibuprofen



The procedure outlined above can likewise be used
 5 for the synthesis of the compounds outlined in Table 5.

Table 5

Compound	R ₈	R ₉	R ₁₀	R ₁₁
 Ibuprofen		COOH	H	H
 Naproxen		COOH	H	H
 Alminoprofen		COOH	H	H
 Fenoprofen		COOH	H	H
 Flurbiprofen		COOH	H	H
 Indoprofen		COOH	H	H

 <p>Ketoprofen</p>		COOH	H	H
 <p>Suprofen</p>		COOH	H	H

EXPERIMENTAL PROCEDURE:

The present invention will now be described in further
 5 detail with reference to the following Example.

1. Preparation of ethyl 3-hydroxy-3-phenylbutanoate.

Ethyl benzoyl acetate (192mg, 1 mmol) was added
 10 to water (10mL, 1mL/g yeast) in a 70 mL Pyrex test tube
 and vortexed until an even dispersion of substrate
 throughout the water was achieved (opaque mixture
 persists). Yeast (10g/mmol) was then added quickly and
 vortex was maintained for a further 5 minutes. This
 15 procedure produced a moist pliable yeast that firmed up a
 few minutes after water had been incorporated into the
 yeast. The reaction was left at room temperature for
 24hours. The product was extracted from the yeast using
 ethyl acetate (2x30 mL). Evaporation under reduced
 20 pressure produced an essentially pure ethyl (S)- 3-
 hydroxy-3-phenylbutanoate as an oil which can be further
 purified by distillation if necessary (isolated yield
 86%) This reaction was repeated several times and
 achieved similar yields.

Unlike a solvent based yeast mediated reduction reaction, there is no interference in the isolation process from extracted biomass material product and
5 therefore chromatographic purification is not needed to obtain pure product; and unlike an aqueous based yeast mediated reduction reaction system, biphasic extractions, often associated with low isolated yields, are avoided.

10 The steps required to synthesise the range of pharmaceutical compounds from the precursors described in this application are will within the skill and knowledge of the person in the art of the invention.

15 The foregoing Examples are provided for illustration of the concept of the invention only. Modifications may be made to the preferred embodiments without departing from the spirit and scope of the invention.

20

Dated this 16th day of October 2003
VICTORIA UNIVERSITY OF TECHNOLOGY
and POLYCHIP PHARMACEUTICALS PTY LIMITED
By their Patent Attorneys

25

GRIFFITH HACK
Fellows Institute of Patent and
Trade Mark Attorneys of Australia

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.